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Representativeness of a Heart Failure Trial by Race and Sex:

Results From ASCEND-HF and GWTG-HF

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Abstract

OBJECTIVES—This study sought to determine the degree to which US patients enrolled in a heart failure (HF) trial represent patients in routine US clinical practice according to race and sex.

BACKGROUND—Black patients and women are frequently under-represented in HF clinical trials. However, the degree to which black patients and women enrolled in trials represent such patients in routine practice is unclear.

METHODS—The ASCEND-HF (Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure) trial randomized patients hospitalized for HF to receive nesiritide or placebo from May 2007 to August 2010 and was neutral for clinical endpoints. This analysis

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APPENDIX For supplemental tables and a Figure, please see the online version of this paper.

compared non-Hispanic white (n = 1,494) and black (n = 1,012) patients enrolled in ASCEND-HF from the United States versus non-Hispanic white and black patients included in a US hospitalized HF registry (i.e., Get With The Guidelines–Heart Failure [GWTG-HF]) during the ASCEND-HF enrollment period and meeting trial eligibility criteria.

RESULTS—Among 79,291 white and black registry patients, 49,063 (62%) met trial eligibility criteria (white, n = 37,883 [77.2%]; black, n = 11,180 [22.8%]). Women represented 35% and 49% of the ASCEND-HF and trial-eligible GWTG-HF cohorts, respectively. Compared with trial-enrolled patients, trial-eligible GWTG-HF patients tended to be older with higher blood pressure and higher ejection fraction. Trial-eligible patients had higher in-hospital mortality (2.3% vs. 1.3%), 30-day readmission (20.2% vs. 16.8%), and 180-day mortality (21.2% vs. 18.6%) than those enrolled in the trial (all; $p < 0.02$), with consistent mortality findings according to race and sex. After propensity score matching, mortality rates were similar; however, trial-eligible patients continued to have higher rates of 30-day readmission (23.1% vs. 17.3%; $p < 0.01$), driven by differences among black patients and women (all p for interaction, ≤0.02).

CONCLUSIONS—Patients with HF seen in US practice and eligible for the ASCEND-HF trial had worse clinical outcomes than those enrolled in the trial. After accounting for clinical characteristics, trial-eligible real-world patients continued to have higher rates of 30-day readmission, driven by differences among black patients and women. Social, behavioral, and other unmeasured factors may impair representativeness of patients enrolled in HF trials, particularly among racial/ethnic minorities and women. (A Study Testing the Effectiveness of Nesiritide in Patients With Acute Decompensated Heart Failure [ASCEND-HF]; NCT00475852).

Keywords

enrollment; heart failure; race; sex; trial

Previous literature has questioned the generalizability of findings from heart failure (HF) trials to the broader HF population seen in routine US practice (1–3). These concerns over generalizability may particularly apply to black patients and women, groups historically under-represented in HF trials relative to their prevalence in US epidemiological cohorts (3–6). However, although the low proportions of these patients within HF trials are well documented, the degree to which black patients and women enrolled in trials reflect their respective populations in clinical practice is unclear. Indeed, it is plausible that under-enrollment of these demographic subsets could lead to exaggerated differences between trial patients and real-world patients. If black patients and women show heightened qualitative differences across trial and clinical practice settings relative to white patients and men, the impact of under-representation on generalizability of trial data would be amplified.

To best ensure clinical trial results meet the needs of the HF community, there is both a need to improve the proportion of black patients and women within trials, and to understand the representativeness of patients from these groups who are ultimately enrolled. To date, studies exploring patient-level differences between trial and real-world HF populations are scarce, and to our knowledge, none has explored the interplay with trial-level under-representation (1,7). A more nuanced understanding of race- and sex-based differences in trial and real-world patients may identify added gaps or bias in the trial enrollment system

and could facilitate development of targeted interventions for clinical trial quality improvement. In this context, a joint analysis of the ASCEND-HF (Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure) randomized clinical trial and the Get With The Guidelines–Heart Failure (GWTG-HF) registry provides a novel opportunity to evaluate the representativeness of trial and real-world patients according to race and sex. Specific comparisons of interest included: 1) trial-ineligible registry patients versus trial-eligible registry patients; 2) trial-eligible registry patients versus patients enrolled in the ASCEND-HF trial; and 3) trial-eligible registry patients versus ASCEND-HF trial patients after accounting for baseline clinical differences.

METHODS

DATA SOURCES.

This analysis used 2 distinct datasets of patients hospitalized for HF: the ASCEND-HF randomized clinical trial and the GWTG-HF registry. The design and primary results of the ASCEND-HF trial have been previously published (8,9). In brief, ASCEND-HF was a prospective, multinational, randomized, placebo-controlled trial studying the effects of nesiritide on dyspnea relief and clinical outcomes among patients hospitalized for acute HF with either reduced or preserved ejection fraction (EF). Eligible patients were enrolled within 24 h of first intravenous HF therapy and had dyspnea at rest or with minimal exertion, ≥1 clinical sign of HF, and ≥1 objective measure of HF. The trial was conducted in accordance with the Declaration of Helsinki and with institutional review board/ethics committee approval at all sites. All patients provided written informed consent.

The GWTG-HF registry is an ongoing, observational, quality improvement program launched in 2005 by the American Heart Association and conducted exclusively in the United States (10). The registry includes patients hospitalized with a primary HF diagnosis. Trained personnel at participating centers use an Internet-based patient management tool (IQVIA, Parsippany, New Jersey) to collect patient-level data on consecutive HF patients admitted to the hospital. All participating centers obtain institutional review board approval for the registry protocol. Given that the primary purpose of the registry is for quality improvement, a waiver for patient informed consent is granted under the Common Rule. To evaluate post-discharge outcomes, registry patients ≥65 years of age with fee-for-service Medicare coverage are linked to Medicare by using a validated technique (11).

STUDY POPULATION AND DESIGN.

The current analysis was limited to ASCEND-HF and GWTG-HF participants identified as non-Hispanic black or non-Hispanic white. To facilitate appropriate comparisons between trial and registry participants, only ASCEND-HF patients enrolled in the United States and GWTG-HF patients with an index hospital admission between May 2007 and August 2010 (i.e., dates of ASCEND-HF trial enrollment) were considered. GWTG-HF patients who left against medical advice or were discharged to hospice, transferred to another hospital, or with missing discharge information were also excluded.

This analysis included 3 parts. In Part 1, GWTG-HF patients eligible for the ASCEND-HF trial were compared with GWTG-HF patients ineligible for the trial. Based on ASCEND-HF trial selection criteria, GWTG-HF patients meeting the following criteria were considered trial ineligible: admission systolic blood pressure <100 mm Hg or >180 mmHg, receiving dopamine/milrinone/dobutamine during index hospitalization, chronic dialysis, moderately severe or severe valvular heart disease (with the exception of mitral regurgitation secondary to ventricular dilation/dysfunction), ventricular assist device, concurrent diagnosis of ischemia/acute coronary syndrome, B-type natriuretic peptide <100 pg/ml or N-terminal pro–B-type natriuretic peptide (NT-proBNP) <125 pg/ml if <75 years of age, NT-proBNP < 425 pg/ml if ≥75 years of age, and admission hemoglobin level <9 g/dl. GWTG-HF patients with none of these exclusion criteria constituted the trial-eligible cohort. In Part 2, GWTG-HF patients determined eligible for ASCEND-HF in Part 1 were compared versus US patients enrolled in the ASCEND-HF trial. In Part 3, comparisons in Part 2 were repeated after accounting for patient characteristics by using propensity score matching.

STUDY ENDPOINTS.

Pre-specified study endpoints included: 1) in-hospital mortality; 2) 30-day all-cause readmission; and 3) 180-day all-cause mortality. In-hospital mortality was assessed among all included patients. For GWTG-HF participants, post-discharge endpoint data were limited to those ≥65 years of age linked to Centers for Medicare & Medicaid Services (CMS) data. Thus, 30-day readmission and 180-day mortality endpoints were assessed and compared only among ASCEND-HF patients ≥65 years of age and GWTG-HF patients linked to Medicare. All clinical endpoint events in ASCEND-HF were confirmed by an independent clinical events committee (University of Glasgow, Glasgow, Scotland). In GWTG-HF, in-hospital mortality events were documented in the case report form; post-discharge mortality was determined by presence of a death date in the CMS beneficiary summary file and post-discharge readmission by examining CMS inpatient claims files for any post-discharge admission to an acute care hospital. To reconcile differences in data capture between ASCEND-HF and GWTG-HF and ensure consistent endpoint definitions, time intervals for post-discharge endpoints were aligned such that the window for 30-day readmission began at index hospital discharge and the window for 180-day mortality began at index hospital admission.

STATISTICAL ANALYSIS.

Baseline characteristics were compared between trial-ineligible, trial-eligible, and trial-enrolled groups by using rank-based standardized differences, with a difference >10 indicating imbalance between groups. To best ensure consistency in data elements and definitions across ASCEND-HF and GWTG-HF datasets, case report forms and data dictionaries from both sources were reviewed; data elements with reasonable alignment were selected a priori for analysis, and data elements without alignment were not reported. Continuous variables were reported as medians (25^{th} to 75th), and categorical variables were reported as frequencies and percentages. Raw event rates for study endpoints were summarized by using counts and percentages.

All comparisons between trial-ineligible (GWTG-HF), trial-eligible (GWTG-HF), and ASCEND-HF–enrolled groups across Parts 1 to 3 were further described within pre-specified demographic subsets: black patients, white patients, women, and men. The p values were generated from Pearson's chi-squared tests, in which each endpoint was assessed in a binary fashion and compared with the corresponding group. Interaction analyses were performed for all study endpoints to test for differential associations between study group and endpoints according to race and sex. Interaction p values were generated from simple logistic regression models on each dichotomized outcome, with models explained by the study group, the variable of interest (e.g., race or sex), and their interaction term. For Part 3, trial-eligible versus trial-enrolled comparisons were performed in propensity score–matched cohorts. Propensity scores were estimated from a logistic model and matched 1:1 by using a greedy 5 to 1 digit-matching algorithm. The following 27 pre-specified baseline variables were included in the logistic model: age, sex, race, EF, systolic blood pressure, heart rate, body mass index, serum creatinine, blood urea nitrogen, serum sodium, medical history (atrial fibrillation/flutter, coronary artery disease, chronic lung disease, cerebrovascular disease/stroke, diabetes, hyperlipidemia, hypertension, and peripheral vascular disease), and background medical and device therapy (beta-blocker, angiotensin-converting enzyme/angiotensin II receptor blocker, mineralocorticoid receptor antagonist, digoxin, loop diuretic, nitrate, hydralazine, implantable cardioverter-defibrillator, and cardiac resynchronization therapy). No imputation was used for missing data.

All statistical analyses were performed by using SAS version 9.4 (SAS Institute, Inc., Cary, North Carolina). Two-tailed p values < 0.05 were considered statistically significant.

RESULTS

TRIAL ELIGIBILITY AND ENROLLMENT ACCORDING TO RACE AND SEX.

Selection of the analytic cohorts and an outline of group comparisons are presented in Figure 1. Overall, 79,291 patients who identified as non-Hispanic black or white race were enrolled in GWTG-HF during the ASCEND-HF recruitment period. Of these patients, 30,228 (38.1%) did not meet ASCEND-HF selection criteria and were ineligible. Among 49,063 patients eligible for ASCEND-HF, 37,883 (77.2%) were white, and 11,180 were black (22.8%); 25,114 (51.2%) were men, and 23,949 (48.8%) were women.

Among 7,141 total patients enrolled in the global ASCEND-HF trial, 2,506 (35.1%) patients were enrolled in the United States and identified as non-Hispanic black or white race. This cohort included 1,012 black patients (40.4%), 1,494 (59.6%) white patients, 1,619 men (64.6%), and 887 (35.4%) women. Proportions of black patients and women were similar among trial-ineligible and trial-eligible patients, whereas patients enrolled in the ASCEND-HF were more frequently black and male (Online Figure 1).

CHARACTERISTICS OF TRIAL-INELIGIBLE VERSUS TRIAL-ELIGIBLE PATIENTS.

Compared with eligible patients, GWTG-HF patients ineligible for ASCEND-HF tended to have higher blood pressure, worse renal function, and lower hemoglobin levels (Tables 1 and 2). With the exception of higher rates of hyperlipidemia among trial-ineligible patients, there

were no significant differences in EF and comorbidities between trial-ineligible and trial-eligible patients. Among patients with HF with reduced EF, rates of guideline-directed therapies were similar or higher among ineligible GWTG-HF patients compared with eligible patients.

Multiple characteristics of trial-ineligible and trial-eligible GWTG-HF patients varied according to race. For example, among black patients, trial-ineligible GWTG-HF patients had higher rates of preserved EF and higher blood pressure (Online Table 1); among white patients, EF and blood pressure were similar between trial-ineligible and trial-eligible patients (Online Table 2). In general, differences in clinical characteristics between trial-ineligible and trial-eligible patients were consistent for men and women (Online Tables 3 and 4).

CHARACTERISTICS OF TRIAL-ELIGIBLE VERSUS TRIAL-ENROLLED PATIENTS.

Compared with trial-eligible GWTG-HF patients, patients enrolled in the ASCEND-HF trial tended to be younger and have lower EF. Having numerous comorbidities was more common among ASCEND-HF patients, including coronary artery disease, hypertension, diabetes, atrial fibrillation/flutter, and peripheral vascular disease. In general, differences in clinical characteristics between trial-eligible GWTG-HF and ASCEND-HF patients did not vary according to race or sex (Online Tables 1 to 4). After propensity score matching, trial-eligible (n = 1,832) and trial-enrolled (n = 1,832) patients were similar across all clinical characteristics (Online Table 5).

HOSPITAL LENGTH OF STAY AND CLINICAL OUT-COMES.

Median (25th to 75th) index hospital length of stay was 4 (3 to 7) days for ineligible GWTG-HF patients, 4 (3 to 7) days for eligible GWTG-HF patients, and 5 (3 to 7 days) for ASCEND-HF patients. Raw event rates for in-hospital mortality, 30-day readmission, and 180-day mortality were consistently highest for trial-ineligible GWTG-HF patients, intermediate for trial-eligible GWTG-HF patients, and lowest for trial-enrolled patients (all $p \leq 0.02$) (Figure 2A). After propensity score matching, there were no significant differences in in-hospital mortality and 180-day mortality between trial-eligible and trial-enrolled patients (all; $p \geq 0.45$) (Figure 2B). In contrast, patients enrolled in the ASCEND-HF trial continued to have significantly lower rates of 30-day readmission (17.3% vs. 23.1%; $p < 0.01$).

CLINICAL OUTCOMES ACCORDING TO RACE AND SEX.

In comparisons of trial-ineligible GWTG-HF patients versus trial-eligible GWTG-HF patients, differences in study endpoints were similar for white and black patients (all p for interaction, ≥0.17) (Figure 3A). Results for in-hospital and 180-day mortality endpoints did vary according to sex, with mortality differences between trial-ineligible and trial-eligible patients larger for men compared with women (all p for interaction, ≤0.04).

In unadjusted comparisons of trial-eligible GWTG-HF patients and ASCEND-HF patients, results for all study endpoints were consistent irrespective of race or sex (Figure 3B). After propensity score matching, significant interactions emerged according to race and sex for

30-day readmission. Compared with ASCEND-HF patients, higher rates of readmission among trial-eligible GWTG-HF patients were driven by events among black patients (29.4% vs. 13.9%) and women (28.0% vs. 16.5%) (all p for interaction, ≤ 0.02) (Figure 3C, Central Illustration). Results for in-hospital and 180-day mortality endpoints did not vary by race or sex after propensity score matching (all p for interaction, ≥0.55).

DISCUSSION

In this patient-level comparison of US patients hospitalized for HF in routine practice and US participants of the ASCEND-HF trial, more than one-third of patients seen in clinical practice were not eligible for trial participation. With few notable exceptions (e.g., blood pressure, renal function), real-world patients who were ineligible and eligible for the trial were generally similar in terms of age, sex, race, and clinical characteristics. In contrast, there were marked differences in clinical profile between trial-eligible real-world patients and those actually enrolled in the trial. Although substantially younger, patients in ASCEND-HF tended to have more comorbidities, lower blood pressure, lower EF, and greater loop diuretic requirements. Despite these high-risk features, compared with trial-eligible and trial-ineligible groups, patients enrolled in ASCEND-HF had significantly lower rates of mortality and readmission. Risk of clinical events increased in stepwise fashion across groups, with trial-eligible patients having intermediate mortality and readmission rates and trial-ineligible patients having the highest rates. After propensity score matching of trial-eligible real-world patients and ASCEND-HF patients, rates of death were similar, but trial-enrolled patients continued to have significantly lower rates of 30-day readmission. Differences in 30-day readmission between eligible and enrolled patients were significantly larger among black patients and women compared with white patients and men.

To our knowledge, this analysis is the first patient-level comparison of trial and real-world HF patients according to race and sex. Previous studies exploring underrepresentation within HF trials have centered on trial-level data outlining the relative enrollment of demographic subgroups relative to prevalence in the general population (4,12). Recognizing that trial-level comparisons do not provide detailed description of patient characteristics and thus may not fully capture gaps in HF trial representativeness, the current joint analysis from GWTG-HF and ASCEND-HF offers several strengths. First, to provide more detailed characterization of patients not enrolled in ASCEND-HF, the trial eligibility criteria were applied to the GWTG-HF population to further stratify patients according to eligibility status. Second, case-report forms and data dictionaries from both registry and trial datasets underwent detailed a priori review to best ensure alignment of relevant data elements and definitions. Likewise, study endpoints were limited to “all-cause” endpoints to minimize influence of data source or adjudication procedures on endpoint results. Further efforts to ensure reliable comparison between registry and trial cohorts included: 1) alignment of the GWTG-HF sample with dates of the ASCEND-HF trial enrollment period; 2) limiting the ASCEND-HF sample to only those enrolled in the United States; and 3) restricting post-discharge outcome analyses to ASCEND-HF patients ≥65 years of age to align with GWTG-HF patients linked to CMS. Third, acknowledging that patient characteristics may still vary within trial eligibility criteria and potentially explain differences in outcomes, eligible and enrolled

patients were further compared by using propensity score matching across 27 pre-specified variables.

By virtue of multiple inclusion and exclusion criteria, US patients enrolled in clinical trials may differ from patients seen in routine practice. However, reasons for these differences may extend beyond objective selection criteria to include the attitudes and perceptions of site investigators and patients (13). Despite meeting formal eligibility criteria, patients may decline participation due to the burden of the protocol, personal preference, or other factors (14). Given the potential of social, economic, and behavioral characteristics to substantially influence patient outcomes, the willingness and ability to provide informed consent and conform to a trial protocol may favor recruitment of a lower risk cohort (14,15). The current analysis from GWTG-HF and ASCEND-HF builds on these themes and provides strong support for the impact of selection bias and unmeasured factors on trial participation. Despite objective biomedical characteristics suggesting that patients in ASCEND-HF were at higher baseline risk than patients in routine practice, rates of mortality and readmission among trial patients were paradoxically lower. Moreover, trial patients continued to experience lower rates of 30-day readmission even when matched to real-world patients similar according to objective baseline measures.

ROLE OF RACE AND SEX IN TRIAL ENROLLMENT AND REPRESENTATIVENESS.

Although social and behavioral characteristics may broadly influence enrollment of all patients, these factors may be particularly relevant to recruitment of racial/ethnic minorities and women. From the patient perspective, it is plausible that differential attitudes, perceptions, and social barriers related to clinical trial participation exist between white men, women, and minorities. Likewise, it is possible that clinicians, investigators, and study coordinators demonstrate conscious or unconscious selection bias regarding trial participation based on sex or race, independent of objective selection criteria (13). In the current study, application of trial eligibility criteria to a broad pool of real-world patients excluded similar proportions of black and white patients, and women and men. However, distributions of race and sex changed markedly during the transition from trial eligible to trial enrolled, consistent with enrollment bias at the patient or site level. Although these relationships may vary with different types and intensities of trial protocols, these findings from ASCEND-HF support the hypothesis that individual patient and local investigator decisions are preeminent factors in determining proportions of minorities and women enrolled, more so than unintended bias from trial selection criteria. Nonetheless, irrespective of the demographic distribution of the enrolled cohort, our findings do support the sizeable impact of selection criteria on shaping the clinical risk of the accrued trial population, with potentially greater impact on mortality risk among men.

Apart from potential influences on overall proportions of minorities and women enrolled, attitudes and perceptions toward trial participation may differentially shape the clinical profile of patients ultimately recruited. In the current study, after propensity score matching, trial-eligible patients continued to exhibit excess rates of 30-day readmission compared with patients successfully enrolled, a finding near exclusively driven by differences among black patients and women. Thus, in relative contrast to white patients and men, black patients and

women enrolled in ASCEND-HF from the United States were not representative of the readmission risk for such patients in routine US practice. These data are consistent with the hypothesis that groups traditionally under-represented in HF trials may also suffer from impaired patient-level representativeness, thus further challenging the ability of trials to inform real-world care of minorities and women (Central Illustration). Further studies are needed in other trial cohorts to confirm these findings and to determine if a consistent relationship between trial-level under-representation and impaired patient-level representativeness emerges. Nonetheless, the current findings from ASCEND-HF should place further impetus on improving enrollment of minorities and women in HF trials. Doing so may require multilevel interventions, such as targeted training for site personnel, site selection in areas with high proportions of minority patients, and reduced burden of trial follow-up procedures to lessen social or economic barriers to participation.

STUDY LIMITATIONS.

First, this case-study comparison of GWTG-HF and ASCEND-HF was performed for hypothesis-generating purposes, and the representativeness of ASCEND-HF may differ compared with other HF trials with different protocols. Likewise, compared with other hospitalized HF trials, ASCEND-HF had fewer selection criteria, a simplified follow-up schedule, and a higher proportion of US enrollment. These features may have attenuated differences between ineligible, eligible, and enrolled US patients in ASCEND-HF relative to other HF trials. Second, despite comprehensive review of data elements and definitions in GWTG-HF and ASCEND-HF and pre-specified inclusion of only those variables with reasonable alignment across databases, it is possible that findings were influenced by differing study definitions and data capture across cohorts. Moreover, lack of alignment across databases and/or missing data required certain potentially important variables to be excluded from propensity score matching (e.g., natriuretic peptide level). This limitation also prevented application of every ASCEND-HF eligibility criterion, and eligibility criteria applied in this study should be considered approximate rather than exact. Similarly, important social determinants of health likely to influence sex and racial representation in clinical trials, such as socioeconomic status, educational level/health literacy, and geography, could not be accounted for in matching methods. Third, it is possible that the rigor and accuracy of data entry by site investigators differed between datasets. Fourth, the degree to which lower event rates among ASCEND-HF patients were affected by patient selection bias versus potentially intensified care/surveillance related to trial participation is unclear. Fifth, black patients were not underrepresented in ASCEND-HF enrollment compared with GWTG-HF, potentially reflecting populations served by different sets of US hospitals.

Previous research supports the national representativeness of GWTG-HF, and thus the current findings suggest relative overrepresentation of black patients in ASCEND-HF (16,17). Larger differences across registry and trial cohorts may have been observed had comparisons included an alternate trial with lower proportional enrollment of black patients. Sixth, it is possible that some trial-eligible GWTG-HF patients may have simultaneously enrolled in the ASCEND-HF trial and that these 2 study groups were not mutually exclusive. Nonetheless, previous data from ASCEND-HF and other HF trials have found US site enrollment rates to be low, reflecting enrollment of only a small proportion of eligible

patients receiving care at each site. Thus, potential overlap between trial-eligible and trial-enrolled groups is likely to be minimal and unlikely to influence the current results.

CONCLUSIONS

HF patients seen in routine US practice and eligible for the ASCEND-HF trial had markedly different characteristics and higher rates of mortality and readmission than those actually enrolled in the trial. After accounting for clinical characteristics, trial-eligible patients continued to have higher rates of 30-day readmission, driven by differences among black patients and women. Unmeasured social and behavioral factors among patients and site investigators may shape the profile of patients enrolled in HF clinical trials, independent of trial eligibility criteria. Such factors may particularly impair the representativeness of black patients and women ultimately enrolled. These findings support the hypothesis that differences between real-world and trial patients may be exaggerated among patients traditionally under-represented in HF trials, and underscore the need to improve enrollment and representativeness of minorities and women to meaningfully inform care of these patients in routine US practice.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS AND ACRONYMS

CMS	Centers for Medicare & Medicaid Services
EF	ejection fraction
GWTG-HF	Get With The Guidelines–Heart Failure
HF	heart failure
NT-proBNP	N-terminal pro– B-type natriuretic peptide

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE 1:

Unmeasured social and behavioral factors among patients and site investigators may shape the profile of patients enrolled in HF clinical trials, independent of trial eligibility criteria. This selection bias legitimizes real-world observational data as separate and distinct from clinical trial data.

COMPETENCY IN MEDICAL KNOWLEDGE 2:

Differences between patients with HF in real-world and clinical trial settings may be exaggerated among patients traditionally underrepresented in HF trials, such as racial/ethnic minorities and women.

TRANSLATIONAL OUTLOOK:

The potential combination of trial-level under-representation and impaired patient-level representativeness challenges the ability of HF trials to inform care of racial/ethnic minorities and women seen in routine practice. This interplay may amplify the impact of trial underrepresentation on the generalizability of trial findings to clinical care. Efforts to improve enrollment and representativeness of racial/ethnic minorities and women in HF trials are needed to ensure that clinical trials meet the needs of the HF community.

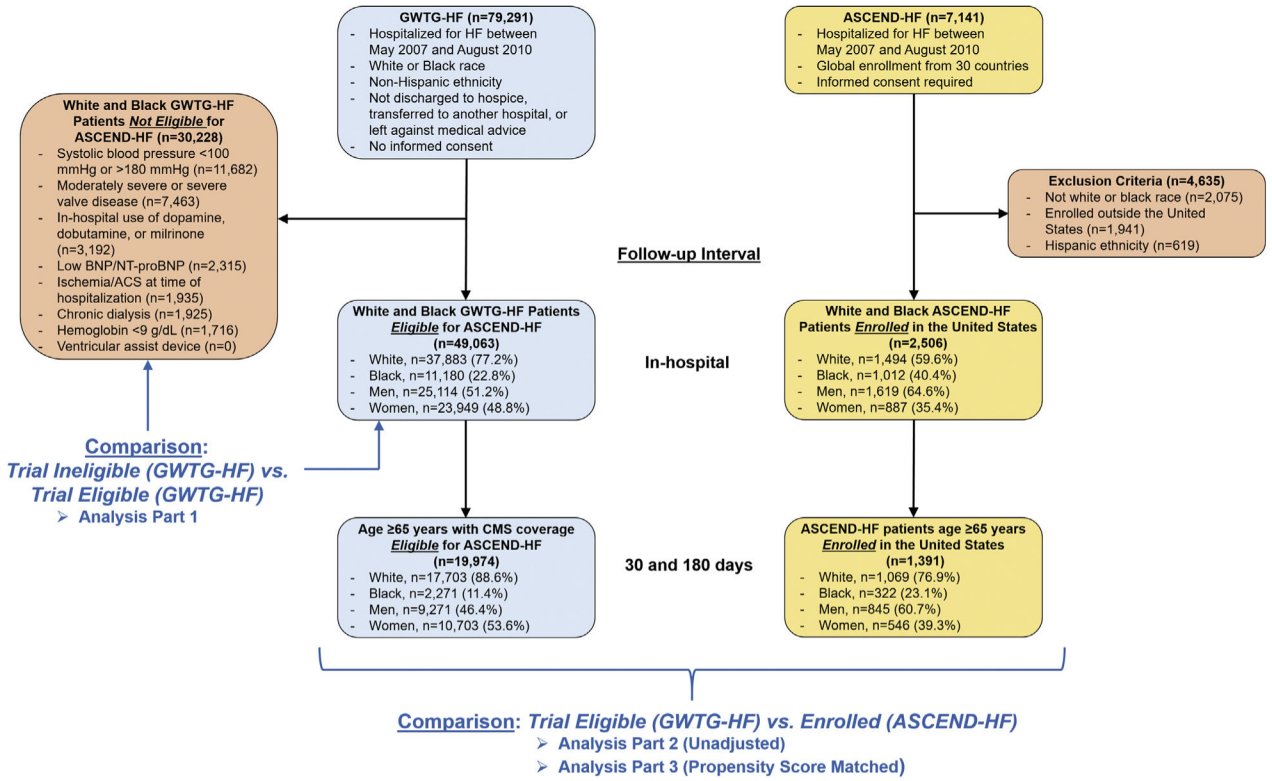


FIGURE 1. Selection of the Analytic Cohorts and Outline of Study Group Comparisons

This study included 3 comparisons: Part 1, trial-ineligible versus trial-eligible patients; Part 2, trial-eligible versus patients enrolled in the trial (unadjusted); and Part 3, trial-eligible versus patients enrolled in the trial (propensity score matched). ACS = acute coronary syndrome; ASCEND-HF = Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure; BNP = B-type natriuretic peptide; CMS = Centers for Medicare & Medicaid Services; GWTG-HF = Get With The Guidelines–Heart Failure; HF = heart failure; NT-proBNP = N-terminal pro–B-type natriuretic peptide.

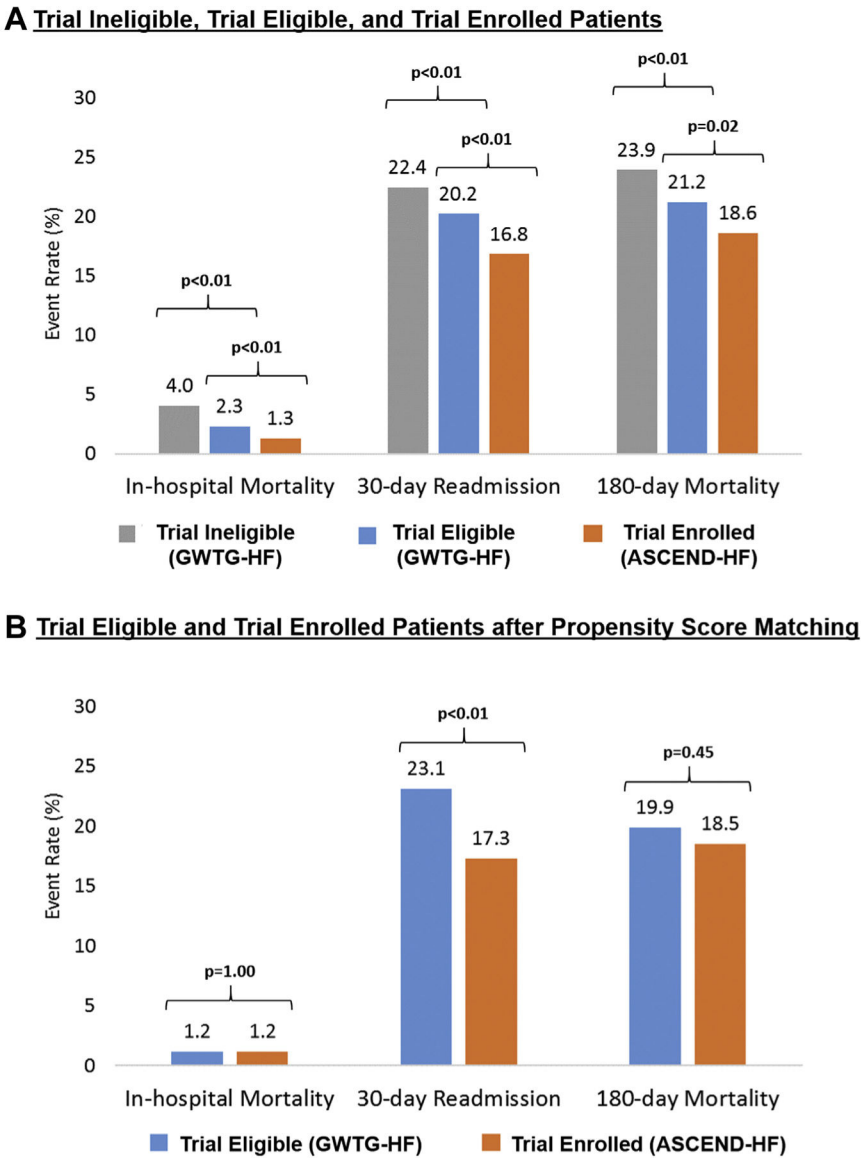


FIGURE 2. In-Hospital and Post-Discharge Outcomes According to Trial Eligibility and Enrollment Status

(A) Event rates for trial-ineligible, trial-eligible, and trial-enrolled patients. **(B)** Event rates for trial-eligible and trial-enrolled patients after propensity score matching. Abbreviations as in Figure 1.

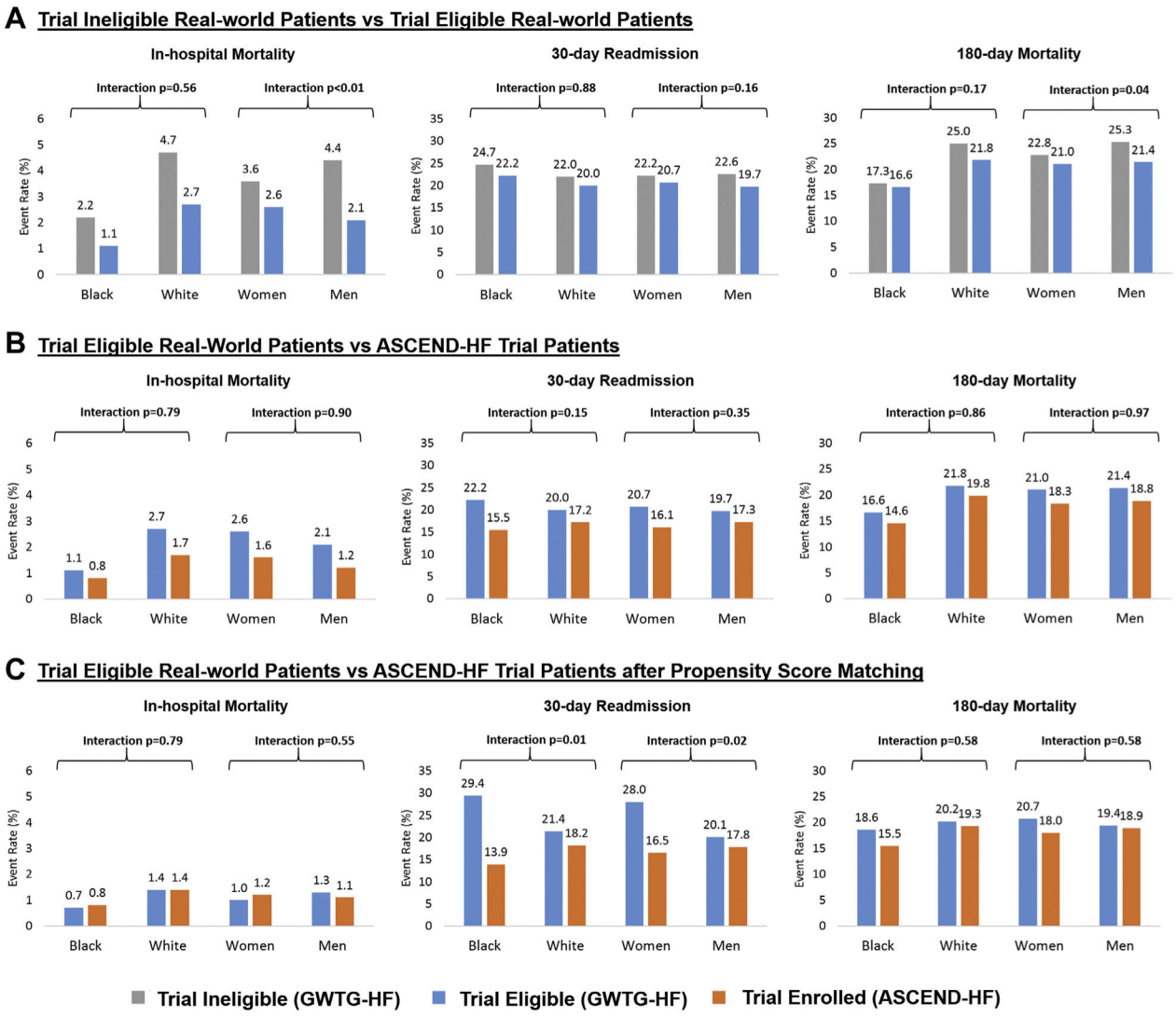
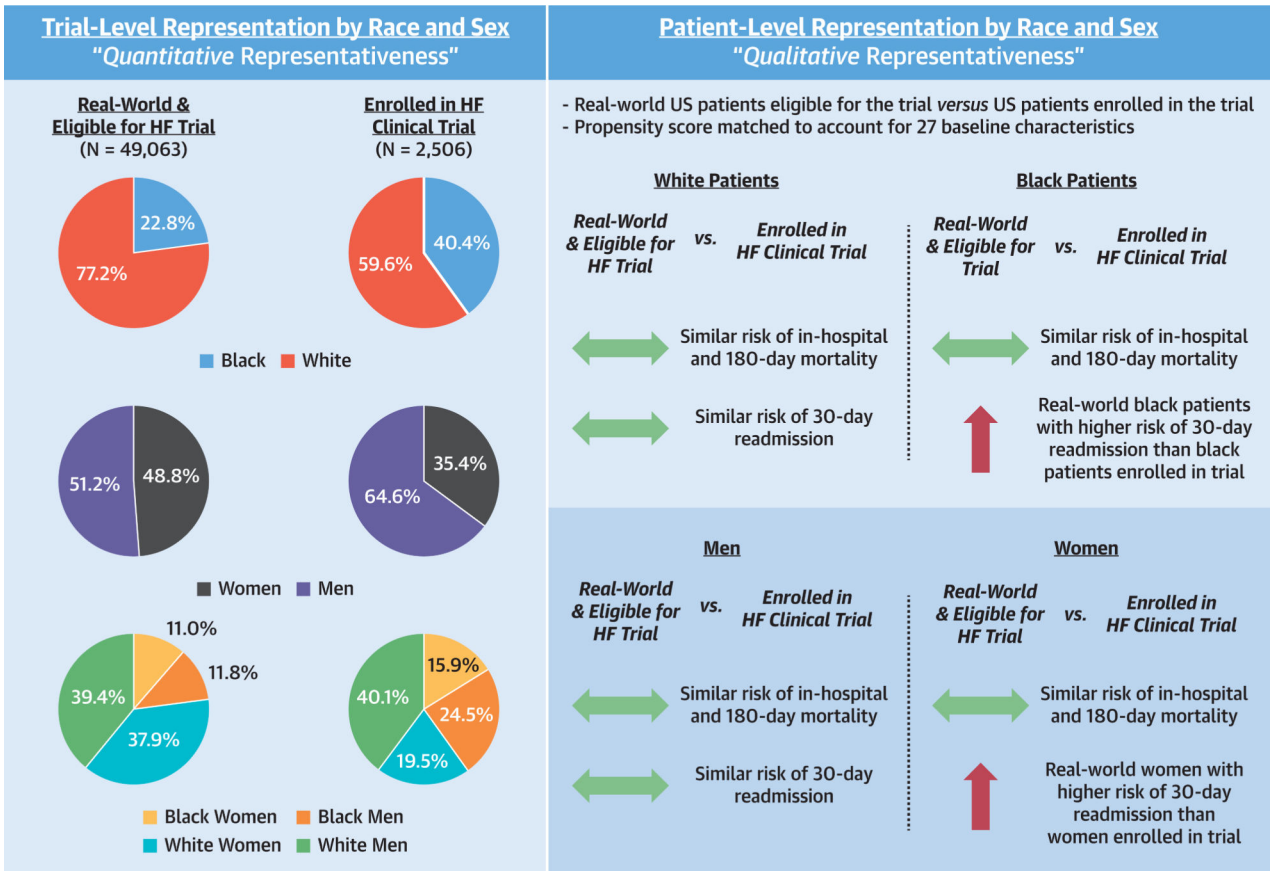


FIGURE 3. Outcomes According To Trial Eligibility And Enrollment Status Stratified According To Race And Sex

The Figure displays event rates for **(A)** trial-ineligible versus trial-eligible patients, **(B)** trial-eligible versus trial-enrolled patients without adjustment, and **(C)** trial-eligible versus trial-enrolled patients after propensity score matching. Abbreviations as in Figure 1.



CENTRAL ILLUSTRATION. Trial- and Patient-Level Representativeness of the ASCEND-HF Trial According to Race and Sex

ASCEND-HF = Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure; HF = heart failure.

TABLE 1

Patient Characteristics Of Trial-Ineligible, Trial-Eligible, And Trial-Enrolled Patients

	GWTG-HF Patients Ineligible for ASCEND-HF (n = 30,228)	GWTG-HF Patients Eligible for ASCEND-HF (n = 49,063)	ASCEND-HF Trial (n = 2,506)	Standardized Differences*	
				GWTG-HF Ineligible Versus Eligible	GWTG-HF Eligible Versus ASCEND-HF
Age, yrs	74 (61–83)	75 (63–84)	67 (55–78)	8.5	46.1
Age ≥65 yrs	20,983 (69.4)	35,408 (72.2)	1,391 (55.5)	6.1	35.2
Women	15,215 (50.3)	23,949 (48.8)	887 (35.4)	3.0	27.4
Race				9.3	38.6
White	22,131 (73.2)	37,883 (77.2)	1,494 (59.6)		
Black	8,097 (26.8)	11,180 (22.8)	1,012 (40.4)		
Ejection fraction, %	40 (25–55)	38 (25–55)	27 (20–40)	5.3	51.4
Ejection fraction >40%	13,322 (47.9)	19,230 (44.0)	479 (23.7)	7.8	44.0
Baseline vital sign and laboratory data					
Systolic blood pressure, mm Hg	140 (113–181)	137 (121–153)	125 (111–142)	10.8	48.1
Heart rate, beats/min	82 (70–97)	82 (70–96)	79 (70–90)	4.4	17.3
Weight, kg	81 (66–99)	82 (68–100)	89 (74–107)	5.5	29.4
BMI, kg/m^2	27.8 (24.4–31.7)	28.0 (26.6–29.5)	30.3 (25.7–35.8)	3.3	32.5
Sodium, mEq/l	138 (135–140)	138 (136–141)	139 (137–141)	8.6	13.1
BNP, pg/ml †	770 (268–1,690)	824 (431–1,610)	1,027 (605–1,830)	14.0	26.4
NT-proBNP, pg/ml ‡	6,059 (2,349–13,118)	4,721 (2,056–10,002)	4,889 (2,295–9,139)	17.1	1.8
BUN, mg/dl	26 (18–41)	24 (17–35)	23 (17–34)	18.9	1.3
Creatinine, mg/dl	1.4 (1.0–2.1)	1.3 (1.0–1.7)	1.3 (1.0–1.7)	23.4	1.8
Hemoglobin, g/dl	11.6 (10.1–13.1)	12.1 (10.8–13.5)	12.3 (11.0–13.6)	28.6	9.3
Medical history					
Coronary artery disease	14,660 (50.1)	19,107 (46.9)	1,517 (60.6)	6.3	27.6
Hypertension	22,815 (77.9)	29,968 (73.6)	2,095 (83.6)	10.1	24.6
Hyperlipidemia	13,706 (46.8)	17,455 (42.9)	1,563 (62.4)	8.0	39.8
Cerebrovascular disease/stroke	4,638 (15.9)	5,485 (13.5)	414 (16.5)	6.7	8.5
Diabetes	12,596 (43.0)	16,439 (40.4)	1,218 (48.6)	5.4	16.6
Atrial fibrillation/flutter	10,119 (34.6)	14,014 (34.4)	1,039 (41.5)	0.3	14.5

	GWTG-HF Patients Ineligible for ASCEND-HF (n = 30,228)	GWTG-HF Patients Eligible for ASCEND-HF (n = 49,063)	ASCEND-HF Trial (n = 2,506)	Standardized Differences*	
				GWTG-HF Ineligible Versus Eligible	GWTG-HF Eligible Versus ASCEND-HF
Peripheral vascular disease	3,928 (13.4)	4,579 (11.3)	401 (16.0)	6.6	13.9
Chronic lung disease	9,006 (30.8)	12,006 (29.5)	648 (25.9)	2.8	8.1
Medical and device therapies before admission (among HFrEF patients only)					
Loop diuretic§	15,845 (58.6)	19,207 (53.1)	1,899 (75.9)	11.2	49.0
ACE inhibitor/ARB	6,928 (53.7)	9,097 (50.8)	1,013 (65.6)	5.8	30.3
Beta-blocker	8,835 (68.5)	11,174(62.4)	1,209 (78.3)	12.7	35.3
MRA	2,022 (15.7)	2,217 (12.4)	443 (28.7)	9.5	41.2
Hydralazine	1,309 (10.1)	1,110 (6.2)	271 (17.5)	14.4	35.6
Nitrate	2,550 (19.8)	2,991 (16.7)	405 (26.2)	7.9	23.3
Digoxin	2,791 (21.6)	3,423 (19.1)	448 (29.0)	6.2	23.3
ICD	4,007 (28.6)	4,690 (23.1)	702 (45.4)	12.8	48.5
CRT	1,069 (7.6)	959 (4.7)	365 (23.6)	12.2	56.3

Values are n (%) or median (25th–75th).

*Standardized difference represents the absolute differences in rank-based means or proportions divided by the SE and multiplied by 100. Standardized differences >10 indicate imbalance between groups.

†B-type natriuretic peptide (BNP) data were available among 20,588 patients in the trial-ineligible group, 24,575 patients in the trial-eligible group, and 1,874 patients in the trial-enrolled group.

‡N-terminal pro–B-type natriuretic peptide (NT-proBNP) data were available among 2,299 patients in the trial-ineligible group, 2,488 patients in the trial-eligible group, and 545 patients in the trial-enrolled group.

§Data reflect the entire sample, irrespective of ejection fraction.

ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; ASCEND-HF = Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure; BMI = body mass index; BUN = blood urea nitrogen; CRT = cardiac resynchronization therapy; GWTG-HF = Get With The Guidelines–Heart Failure; HFrEF = heart failure with reduced ejection fraction; ICD = implantable cardioverter-defibrillator; MRA = mineralocorticoid receptor antagonist.

TABLE 2

Patient Characteristics of Trial-Ineligible, Trial-Eligible, and Trial-Enrolled Patients (GWTG-HF Linked to CMS and ASCEND-HF Age ≥65 Years)

	GWTG-HF Patients Ineligible for ASCEND-HF (n = 11,773)	GWTG-HF Patients Eligible for ASCEND-HF (n = 19,974)	ASCEND-HF Trial (n = 1,391)	Standardized Differences*	
				GWTG Ineligible Versus Eligible	GWTG Eligible Versus ASCEND-HF
Age, yrs	80 (73–86)	81 (74–86)	77 (71–83)	5.7	39.9
Women	6,562 (55.7)	10,703 (53.6)	546 (39.3)	4.3	29.0
Race				8.2	31.6
White	10,111 (85.9)	17,703 (88.6)	1,069 (76.9)		
Black	1,662 (14.1)	2,271 (11.4)	322 (23.2)		
Ejection fraction, %	45 (30–57)	43 (30–56)	30 (21–49)	5.2	46.2
Ejection fraction >40%	5,905 (55.0)	9,108 (51.9)	363 (32.3)	6.3	40.4
Baseline vital sign and laboratory data					
Systolic blood pressure, mm Hg	140 (115–181)	138 (122–153)	126 (112–142)	11.7	49.2
Heart rate, beats/min	80 (69–94)	80 (69–93)	76 (68–86)	3.1	22.8
Weight, kg	77 (63–91)	77 (64–92)	83 (70–98)	4.6	26.7
BMI, kg/m^2	27.1 (24.2–30.9)	27.3 (25.8–29.2)	28.7 (24.8–33.0)	8.8	19.7
Sodium, mEq/L	138 (136–141)	138 (136–141)	139 (137–141)	4.3	15.6
BNP, pg/ml†	771 (334–1,590)	772 (414–1,480)	1,057 (639–1,898)	7.1	38.7
NT-proBNP, pg/ml‡	6,149 (2,260–14,019)	5,118 (2,167–10,598)	5,720 (2,801–10,790)	11.5	11.7
BUN, mg/dl	27 (19–40)	25 (18–36)	27 (19–38)	15.4	18.0
Creatinine, mg/dl	1.4 (1.0–2.0)	1.3 (1.0–1.7)	1.4 (1.1–1.8)	18.6	10.5
Hemoglobin, g/dl	11.6 (10.1–13.0)	11.9 (10.7–13.2)	12.0 (10.8–13.3)	23.4	4.2
Medical history					
Coronary artery disease	6,256 (54.6)	8,485 (50.5)	1,030 (74.1)	8.3	50.2
Hypertension	1,183 (85.1)	12,437 (74.0)	1,183 (85.1)	9.6	27.7
Hyperlipidemia	5,673 (49.5)	7,443 (44.3)	991 (71.2)	10.5	56.8
Cerebrovascular disease/stroke	2,001 (17.5)	2,531 (15.1)	271 (19.5)	6.5	11.7
Diabetes	4,724(41.2)	6,329 (37.6)	687 (49.4)	7.3	23.9
Atrial fibrillation/flutter	4,677 (40.8)	6,670 (39.7)	775 (55.7)	2.3	32.6
Peripheral vascular disease	1,781 (15.5)	2,164 (12.9)	297 (21.4)	7.7	22.7

	GWTG-HF Patients Ineligible for ASCEND-HF (n = 11,773)	GWTG-HF Patients Eligible for ASCEND-HF (n = 19,974)	ASCEND-HF Trial (n = 1,391)	Standardized Differences*	
				GWTG Ineligible Versus Eligible	GWTG Eligible Versus ASCEND-HF
Chronic lung disease	3,411 (29.8)	4,855 (28.9)	392 (28.2)	2.0	1.5
Medical and device therapies before admission (among HFrEF patients only)					
Loop diuretic§	6,379 (59.5)	8,133 (53.0)	1,073 (77.2)	13.0	52.5
ACE inhibitor/ARB	2,367 (53.6)	3,240 (49.8)	475 (62.5)	7.6	25.8
Beta-blocker	3,026 (68.6)	4,098 (63.0)	603 (79.3)	11.7	36.7
MRA	546 (12.4)	593 (9.1)	157 (20.6)	10.5	32.8
Hydralazine	324 (7.3)	322 (5.0)	100 (13.1)	10.0	28.8
Nitrate	863 (19.6)	1,158 (17.8)	192 (25.2)	4.5	18.1
Digoxin	929 (21.0)	1,277(19.6)	195 (25.6)	3.5	14.4
ICD	1,103 (23.4)	1,410 (19.7)	345 (45.3)	9.1	56.9
CRT	304 (6.5)	266 (3.7)	209 (27.5)	12.5	69.3

Values are n (%) or median (25th–75th percentile).

*Standardized difference represents the absolute differences in rank-based means or proportions divided by the SE and multiplied by 100. Standardized differences >10 indicate imbalance between groups.

†BNP data were available among 8,274 patients in the trial-ineligible group, 10,684 patients in the trial-eligible group, and 1,067 patients in the trial-enrolled groups.

‡NT-proBNP data were available among 893 patients in the trial-ineligible group, 998 patients in the trial-eligible group, and 292 patients in the trial-enrolled group.

§Data for loop diuretic use reflect the entire sample, irrespective of ejection fraction.

CMS = Centers for Medicare & Medicaid Services; other abbreviations as in Table 1.